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COURTESY COPY OF THE INTERNATIONAL

PRELIMINARY EXAMINATION REPORT

WITH ANNEXES CONTAINING

PAGES 3, 3a, 5, AND 6 TO BE

SUBSTITUTED FOR ORIGINAL

SPECIFICATION PAGES 3, 5, AND 6

AND CLAIMS 1-14 TO BE SUBSTITUTED

FOR ORIGINAL CLAIMS 1-14

FOR EXAMINATION IN THIS CASE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 143019.8SB	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IL 03/00205	International filing date *(day/month/year)* 13.03.2003	Priority date *(day/month/year)* 13.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/00		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.09.2003	19.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Koessler, J-L Telephone No. +49 89 2399-7217

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00205

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 4, 7-20	as originally filed
3, 3a, 5, 6	received on 19.04.2004 with letter of 19.04.2004

Claims, Numbers

1-14	received on 19.04.2004 with letter of 19.04.2004

Drawings, Sheets

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14 (partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The present application had only a partial search report drawn up because of lack of unity. Furthermore, only two examination fees were paid. Hence, the present communication relates only to the subject-matter indicated by the applicant i.e. compound of formula I wherein n is 1, X is NHR, X' is H and Y is OR1, the use thereof for the preparation of a medicament and a pharmaceutical composition comprising said compound (claims 1-14 partially) and compounds of formula I wherein n is 1, X is NHR, X' is CH2OH and Y is OR1, the use thereof for the preparation of a medicament and a pharmaceutical composition comprising said compound (claims1-14 partially). The Applicant is invited to restrict the claims to said subject-matter and to adapt the description accordingly.

2. Amendments (Art. 34(2) PCT)

The Applicant restricted the subject-matter of new claim 1 to compounds of formula (I) wherein n is 1. Nevertheless he did not further restrict the subject-matter of claim 1 concerning the definition of X, X' and Y (see item III).

The Applicant deleted the following disclaimer: X = X' = H and n = 0, Y is not OR_1 wherein R_1 is H, alkyl or aryl which do no longer fall under the scope of new claim 1 (cf n = 1).

The Applicant however introduced to new disclaimers:
- X and X' can not be at the same time H. The Applicant introduced this to exclude compound 7 of D1 and compound 6 of D2 (which are in fact the same compound). Accordingly, the Applicant deleted compound i, j from original claim 5 and 12. This disclaimer is useless since this compound does not fall under the scope of the present examination report (see item III). The Applicant is reminded that he did not pay the search fees for the invention(s) wherein X and X' is H and hence this subject-matter need not be the subject of an international preliminary examination (R. 66(1)e).
- when X is NH-R where R is a linear or branched acyl Y is not OR_1 for R_1 being a 4-nitrophenyl. This disclaimer has been introduced to exclude compound 8 of D1 and compound 6 of D2 (which are in fact the same compound). This disclaimer is not acceptable under Art. 34(2) PCT. The subject-matter of a disclaimer should be strictly limited in scope in order to exclude only the accidental novelty destroying compound(s). This disclaimer could be acceptable if R is Ac. Hence, new claim 1 is not acceptable under Art. 42(2) PCT.

The Applicant adapted the corresponding part of the description (p. 5, 6) to new claim 1.

The Applicant deleted "substantially as described in the specification from claim 13.

New pages 3 and 3a wherein the Applicant pretends having acknowledged D1-D3 are certainly erroneous.

3. Novelty (Art. 33(2) PCT)

The present application relates to 1,3-cyclic propanediol phosphate derivatives pharmaceutical composition thereof and the use of said derivatives as cell stimulants.

D1 and D2 relate to antibody catalyzed hydrolysis of a phosphotriester.

D3 is directed towards prodrugs of substituted cyclic 1,3-propanyl phosphate, phosphonate and phosphoramidate ester compounds which in their active form have a phosphate, phosphonate, or phosphoramidate group, to their preparation, to their synthetic intermediates, and to their use. D3 does not describe compounds of formula (I) wherein X' is CH_2OH. Although the rest of the compounds claimed in the present application fall under the scope of the claims of D3, this document does not describe explicitly any compounds which fall under the scope claim 1 of the present application.

None of the cited documents describe explicitly a compound which falls under the scope of new claim 1. Hence, the present application meets the requirements of Art. 33(2) PCT because the subject-matter of claims 1-14 is not novel.

4. Inventive step (Art. 33(3) PCT)

The closest prior art is considered to be document D3.

The problem underlying the present application is to be regarded as to provide alternative cyclic glycerophosphate derivatives, pharmaceutical compositions thereof and the use of said derivatives for the preparation of a medicament.

The Applicant in his reply argues that the compounds of D3 have a polyphosphate group. But D3 recites (claim 1): "M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$ is biologically active". This does not mean that M possess such a mono, di, or triphosphate group. However the compound of D3 are prodrugs for treating cancer (claim 243), viral infections (claim 248), liver fibrosis

(claim 256), hyperlipidaemia (claim 257) and parasitic infections (claim 260) whereas the compounds of the present application are useful in the treatment of diseases or deficiencies related to neural cell activity.

None of the cited documents nor a combination of the teaching would fairly suggest that the compounds of formula (I) are neural cell stimulants.

Therefore, the present application meets the requirements of Art. 33(3) PCT because the subject-matter of claims 1-14 is inventive.

5. Industrial applicability (Art. 33(4) PCT)

The subject-matter of claims 1-14 is considered to be industrially applicable.

6. Clarity (Art. 6 PCT)

The embodiments of the invention described on pages 15 (examples 10 and 11) do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

The applicant is requested to remove the inconsistency by deleting the "excess" subject-matter from the description or by indicating in the description that the embodiments concerned do not form part of the invention but represent background art that are useful for understanding the invention (see the PCT Guidelines, III-4.3).

7. Other defects of the application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

10/507490
DT04 Rec'd PCT/PTO 13 SEP 2004

X' is hydrogen or CH_2OH;

Y is O-R_1, NH-R_1;

R is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl or araalkyl residue;

R_1 is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substiuted aryl, alkylcarboxy ester or alkyl-N-R_2R_3;

R_2 and R_3 are independently hydrogen or an alkyl group;

provided that X and X' can not both be hydrogen; when X is NH-R where R is a linear or branched acyl Y is not OR_1 for R_1 being a 4-nitrophenyl; and provided that when X' is CH_2OH then X is NH-R or NO_2.

As used herein the term *"alkyl"* refers to an alkyl group having from 1 to 24 carbon atoms, e.g. preferably from 3 carbon atoms to 20 carbon atoms, most preferably from 5 carbon atoms to 15 carbon atoms; the term *"acyl"* refers to an aliphatic saturated or unsaturated C_1 - C_{24} acyl group, preferably an acyl group having an even number of carbon atoms, most preferably an acyl group derived from a natural fatty acid such as a saturated aliphatic acyl group selected from acetyl, butyryl, caproyl, octanoyl, decanoyl, lauroyl, myristyl, palmitoyl and stearoyl, or an unsaturated aliphatic acyl group selected from palmitoleyl, oleyl, linoleyl, and ricinoleyl; and the term *"aryl"* refers to a mono- or poly-carbocyclic aryl group, most preferably phenyl, optionally substituted by C_1 - C_4 alkyl, halogen and/or hydroxy.

In one embodiment, Y is a hydroxyl group and X is O-oleoyl, O-benzyl, O-$CH_2COOCH_2CH_3$, NH-benzyl or NH-caproyl.

In another embodiment X is hydrogen and Y is O-acetyl or NH-CH_3.

The present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I. A preferred use of said composition is for stimulation of target cells.

The *CPP* used in the invention may exert one of many neural promoting activities including but not limited to promotion of neuronal outgrowth, promotion

tyrosine hydroxylase (TH), the key enzyme in the dopamine production pathway immunoreactvity when treated with factors like GDNF (Tomac, A. *et al.* 1995) and ciliary neurotrophic factor (CNTF) (Hagg, T. and Varon 1993).

ameliorating or preventing the enhancement of the treated condition and related symptoms.

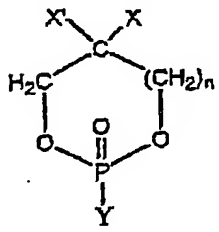
Neural promoting activity – this term encompasses a variety of neural related activities which may be promoted in target cells upon their contact with the *CPP* used in the invention. Such activities include but are not limited to promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased brain, prevention of nerve degeneration, and nerve rescue.

Prevention or treatment – the term prevention of disorders or diseases is to be understood in accordance with the invention as a reduction in the probability of the appearance of such disorders or diseases in an individual having a high predisposition of developing such disorders or diseases, reducing the extent of the symptoms associated with such disorders and diseases when they occur or completely preventing their appearance.

SUMMARY OF THE INVENTION

In accordance with the invention new derivatives of 1,3-cyclic propandiol phosphate are provided that are capable of stimulating cells.

The present invention thus provides, by a first of its aspects, a compound of formula I



or pharmaceutically acceptable salts thereof,

wherein

n is 1;

X is hydrogen, O-R, NH-R, NO_2, or N-(C=O)-R;

X' is hydrogen or CH_2OH;

Y is O-R_1, NH-R_1;

R is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl or araalkyl residue;

R_1 is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl, alkylcarboxy ester or alkyl-N-R_2R_3;

R_2 and R_3 are independently hydrogen or an alkyl group;

provided that X and X' can not both be hydrogen; when X is NH-R where R is a linear or branched acyl Y is not OR_1 for R_1 being a 4-nitrophenyl; and provided that when X' is CH_2OH then X is NH-R or NO_2.

As used herein the term *"alkyl"* refers to an alkyl group having from 1 to 24 carbon atoms, e.g. preferably from 3 carbon atoms to 20 carbon atoms, most preferably from 5 carbon atoms to 15 carbon atoms; the term *"acyl"* refers to an aliphatic saturated or unsaturated C_1 - C_{24} acyl group, preferably an acyl group having an even number of carbon atoms, most preferably an acyl group derived from a natural fatty acid such as a saturated aliphatic acyl group selected from acetyl, butyryl, caproyl, octanoyl, decanoyl, lauroyl, myristyl, palmitoyl and stearoyl, or an unsaturated aliphatic acyl group selected from palmitoleyl, oleyl, linoleyl, and ricinoleyl; and the term *"aryl"* refers to a mono- or poly-carbocyclic aryl group, most preferably phenyl, optionally substituted by C_1 - C_4 alkyl, halogen and/or hydroxy.

In one embodiment, Y is a hydroxyl group and X is O-oleoyl, O-benzyl, O-$CH_2COOCH_2CH_3$, NH-benzyl or NH-caproyl.

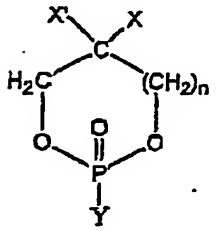
In another embodiment X is hydrogen and Y is O-acetyl or NH-CH_3.

The present invention further provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as an active ingredient, a compound of the general formula I. A preferred use of said composition is for stimulation of target cells.

The *CPP* used in the invention may exert one of many neural promoting activities including but not limited to promotion of neuronal outgrowth, promotion

CLAIMS:

1. A compound of the following formula (I):



or pharmaceutically acceptable salts thereof,

wherein:

n is 1;

X is hydrogen, O-R, NH-R, NO_2, or N-(C=O)-R;

X' is hydrogen or CH_2OH;

Y is O-R_1, NH-R_1;

R is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl or araalkyl residue;

R_1 is hydrogen, linear or branched alkyl, linear or branched acyl, substituted or non-substituted aryl, alkylcarboxy ester or alkyl-N-R_2R_3;

R_2 and R_3 are independently hydrogen or an alkyl group;

alkyl is an alkyl group having from 1 to 24 carbon atoms, preferably from 3 carbon atoms to 20 carbon atoms, most preferably from 5 carbon atoms to 15 carbon atoms;

wherein acyl is an aliphatic saturated or unsaturated C_1 - C_{24} acyl group, preferably an acyl group having an even number of carbon atoms, and most preferably an acyl group derived from a natural fatty acid such as a saturated aliphatic acyl group or an unsaturated aliphatic acyl group;

aryl is a to a mono- or poly-carbocyclic aryl group, most preferably phenyl, optionally substituted by C_1-C_4 -alkyl, halogen and/or hydroxy;

provided that X and X' can not both be hydrogen; when X is NH-R where R is a linear or branched acyl Y is not OR_1 for R_1 being a 4-nitrophenyl; and further provided that when X' is CH_2OH then X is NH-R or NO_2.

2. A compound according to claim 1, wherein the acyl moiety is selected from the group comprising of acetyl, butyryl, caproyl, octanoyl, decanoyl, lauroyl, myristyl, palmitoyl and stearoyl, palmitoleyl, oleyl, linoleyl, and ricinoleyl.

3. A compound according to claim 1 wherein Y is OH and X is O-R or NH-R; wherein R is a linear or branched alkyl or linear or branched acyl.

4. A compound according to claim 1 wherein X is hydrogen and Y is $O\text{-}R_1$ or $NH\text{-}R_1$; wherein R_1 is a linear or branched acyl.

5. Compounds of formula I according to claim 1 selected from the group consisting of:

(a) 1,3-cyclic propandiol phosphate-5-oleoyl;

(b) 1,3-cyclic propandiol phosphate-5- benzyloxy;

(c) 1,3-cyclic propandiol phosphate-5- benzylamino;

(d) 1,3-cyclic propandiol phosphate-5- caproylamido;

(e) 1,3-cyclic propandiol phosphate-2-benzyloxy;

(f) 1,3-cyclic propandiol phosphate-2- acetyloxy;

(g) 1,3-cyclic propandiol phosphate-2-methylamino;

(h) 1,3-cyclic propandiol phosphate-5-glycine ethylester;

(i) 2-dimethylamine ethyl ester 1,3-cyclic propanediol phosphate;

(j) 1,3-cyclic propanediol phosphoamidate;

(k) 1,3-cyclic propanediol N-ethyl phosphoamidate;

(l) 1,3-cyclic propanediol phosphoamidate glycine ethylester;

(m) 2-benzyloxy 1,3-chloropropanediol phosphate;

(n) 2-caproimido 1,3-chloropropanediol phosphate;

(o) 5-amino-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

(p) 5-nitro-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

or pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising a pharmaceutical acceptable carrier and, as an active ingredient, a compound of the general formula (I) in claim 1 or pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 6, for promoting neural activity.

8. A pharmaceutical composition according to claim 7, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.

9. A pharmaceutical composition according to claim 8, wherein said neuronal outgrowth is axonal growth or axonal branching.

10. A pharmaceutical composition according to claim 6, for the prevention or treatment of disorders and diseases which can be prevented or treated by activating neural cells.

11. A pharmaceutical composition according to claim 8, wherein said disorder and disease are schizophrenia, dementia or disorder resulting from learning disabilities.

12. A pharmaceutical composition according to any one of claims 6 to 11 wherein the compound of formula I is selected from the group consisting of

(a) 1,3-cyclic propandiol phosphate-5-oleoyl;

(b) 1,3-cyclic propandiol phosphate-5- benzyloxy;

(c) 1,3-cyclic propandiol phosphate-5- benzylamino;

(d) 1,3-cyclic propandiol phosphate-5- caproylamido;

(e) 1,3-cyclic propandiol phosphate-2-benzyloxy;

(f) 1,3-cyclic propandiol phosphate-2- acetyloxy;

(g) 1,3-cyclic propandiol phosphate-2-methylamino;

(h) 1,3-cyclic propandiol phosphate-5-glycine ethylester;

(i) 2-dimethylamine ethyl ester 1,3-cyclic propanediol phosphate;

(j) 1,3-cyclic propanediol phosphoamidate;

(k) 1,3-cyclic propanediol N-ethyl phosphoamidate;

(l) 1,3-cyclic propanediol phosphoamidate glycine ethylester;

(m) 2-benzyloxy 1,3-chloropropanediol phosphate;

(n) 2-caproimido 1,3-chloropropanediol phosphate;

(o) 5-amino-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

(p) 5-nitro-5-hydroxymethyl-2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-ol;

or pharmaceutically acceptable salts thereof.

13. Use of a compound of formula I for the preparation of a medicament for treating disorders and diseases which can be prevented or treated by activating neural cells.

14. Use according to claim 13, wherein said neural activity is selected from the group consisting of promotion of neuronal outgrowth, promotion of nerve growth, provision of dopaminotrophic supporting environment in a diseased portion of the brain, prevention of nerve degeneration and nerve rescue.